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ORIGINAL RESEARCH

Residual Limb Hyperhidrosis and RimabotulinumtoxinB: A Randomized Placebo-Controlled Study

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Abstract

Objective: To investigate the use of rimabotulinumtoxinB (BoNT/B [Myobloc]) compared with placebo in treating hyperhidrosis in the residual limbs of individuals with amputation.

Design: Randomized, double-blind, placebo-controlled pilot study.

Setting: Military medical center.

Participants: Male participants (N=9) with 11 major amputations of the lower limbs and who complained of excessive sweating in their residual limbs were enrolled in the study between September 24, 2008 to October 28, 2011. Participants' lower limbs were randomly assigned to receive injections of either BoNT/B (n=7) or placebo (n=4).

Intervention: BoNT/B.

Main Outcome Measures: The primary efficacy variable was a minimum of 50% reduction in sweat production 4 weeks after the injection as measured via gravimetric sweat analysis after 10 minutes of physical exertion. Secondary analyses were performed on prosthetic function and pain.

Results: All volunteers (100%; 7) in the BoNT/B group achieved a minimum of 50% reduction in sweat production as compared with only 50% (2) in the placebo group. The percent reduction was significantly greater for the BoNT/B group than for the placebo group (−72.7%±15.7% vs −32.7%±39.2%; $P<.05$). Although both groups subjectively self-reported significant sweat reduction and improved prosthetic function ($P<.05$ for both), objective gravimetric sweat analyses significantly decreased only for the BoNT/B group (2.3±2.3g vs 0.7±1.1g; $P<.05$). Neither group reported a change in phantom limb pain or residual limb pain ($P>.05$ for both).

Conclusions: BoNT/B successfully reduces sweat production in individuals with residual limb hyperhidrosis, but does not affect pain. No differences were found in perceived effect on prosthetic use between BoNT/B and placebo groups.

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Since the beginning of the conflicts in Iraq and Afghanistan, >1600 service members have sustained an amputation of ≥1 limbs as a result of combat-related wounds.[1] Most of these wounded warriors now use upper and/or lower limb prostheses to support independence, including activities of daily living and mobility, as well as vocational and avocational participation. Despite the advancement in prosthetic materials and components over the past decade, 23% to 56% of individuals with limb loss report excessive sweating (hyperhidrosis) of their residual limb(s) that severely impedes their use of prostheses.[2-4] The prevalence of hyperhidrosis in individuals with limb loss is likely a result of decreased body surface area, leading to inefficient heat

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dissipation, although it is unclear what determines whether an individual will experience hyperhidrosis.[5] The use of prosthetic sockets and liners has been shown to contribute to hyperhidrosis because the portion of the residual limb in contact with the prosthesis is isolated from the outer environment, preventing sweat evaporation or skin cooling.[6] In addition, residual limb sweating can contribute to excessive skin moisture, which when coupled with shear and stress forces within a rigid prosthetic socket, as well as the stasis of sweat within the socket, may lead to secondary problems such as skin breakdown, dermatitis, and infection. This may also result in decreased prosthetic use or even prosthetic abandonment.[7] Patients with limb amputation report that the greatest dissatisfaction and frustration with their prostheses is due to excessive sweating.[2,8] Therefore, the primary and secondary effects of residual limb hyperhidrosis may have a significant negative impact on function and quality of life in individuals with limb loss.

Current treatment options for residual limb sweating are less than optimal. Antiperspirants or other topical agents, such as aluminum chloride, must be reapplied frequently and may increase skin irritation. Oral pharmacological management with anticholinergic medications has limited efficacy because of unwanted side effects, such as dry mouth, tachycardia, and impaired concentration and memory.[9-11] Surgical procedures, including endoscopic sympathectomy and sweat gland excision, are reserved for extreme cases of hyperhidrosis and are often accompanied by scars, infection, or restricted limb movement.[12,13] Therefore, there remains the need for a way to effectively treat hyperhidrosis at a limited cost to the patient.

Comparatively, numerous case studies[5,14,15] have corroborated reduced focal hyperhidrosis and thus improved fit and function of prostheses after treatment with onabotulinumtoxinA (BoNT/A). An alternative serotype to BoNT/A is rimabotulinumtoxinB (BoNT/B [Myobloc]). BoNT/B has been demonstrated to be effective in reducing axillary and palmar hyperhidrosis.[16,17] The toxin functions to decrease sweating by blocking the release of acetylcholine from postganglionic sympathetic fibers in the sweat glands.[18] Treatment of hyperhidrosis by BoNT/B is an off-label use of the Food and Drug Administration–approved drug, but it may be preferable to BoNT/A because of its wider radius of diffusion, faster rate of onset, and higher affinity for autonomic nerves.[19-21] BoNT/B has shown similar efficacy to BoNT/A in reducing palmar and residual limb hyperhidrosis in individuals with amputation, as well as greater efficacy than that of BoNT/A in decreasing phantom limb pain (PLP) and residual limb pain (RLP).[22-24] A case series by Kern et al[22] of 9 lower limb amputees receiving 1750U BoNT/B injections at the site of maximum sweating reported a reduction in residual limb sweating, which also contributed to significant improvements in the use of prosthetic devices, steadiness of gait, quality of life, and work performance. They further reported a decrease in RLP in 8 of 9 participants.

However, previous studies of BoNT/B treatment of residual limb hyperhidrosis, including the pilot study by Kern,[22] have relied on subjective self-reporting of sweat reduction. To date, no published studies have objectively measured sweat production in the amputee population pre- and post-BoNT/B treatment. Given the current lack of empirical data and absence of completed placebo-controlled trials, we sought to assess via gravimetric analysis whether BoNT/B treatment of individuals with lower limb amputation causes a greater reduction in hyperhidrosis than does placebo. Unlike surveys that rely on self-reported values, gravimetric analysis quantifies the actual amount of sweat produced during a specific period of time spent executing a controlled activity.[25] Gravimetric analysis is less expensive than water evaporation measurement methods, such as transepidermal water loss, because it requires only the use of a filter paper and a scale, and it can be more reliable than staining procedures for sweat visualization.[25]

Thus, we aimed to reliably assess the effect of BoNT/B injections on residual limb hyperhidrosis after amputation. Secondarily, we report on PLP and RLP after BoNT/B treatment.

List of abbreviations:

BoNT/A	**onabotulinumtoxinA**
BoNT/B	**rimabotulinumtoxinB**
PLP	**phantom limb pain**
RLP	**residual limb pain**
VAS	**visual analog scale**

Methods

Participants

After institutional review board approval from the Walter Reed Army Medical Center, Washington, DC, which is now a part of Walter Reed National Military Medical Center, Bethesda, MD, a total of 9 participants with 11 lower limb amputations were enrolled in the study. The threshold criterion for study entry was a complaint of excessive sweating that negatively affected the fit and/or function of the prosthesis. *Excessive sweating* was defined as focal, visible sweating in the region of the residual limb. Participants were excluded if they had inflammation, skin grafts, open wounds, rashes, or other skin conditions in the residual limb; any medical conditions that placed participants at increased risk with exposure to BoNT/B; any systemic medical conditions that were not medically managed or controlled at the time of recruitment; and any condition or situation that, in the investigator's opinion, may have confounded the study results, including current or planned use of aminoglycosides or preexisting medical conditions that affect body temperature regulation. Participants provided written informed consent before enrollment in the study.

Procedures

The 11 lower limbs of the 9 participants were randomly assigned to receive injections of either BoNT/B (n=7) or placebo (n=4) by a computer-generated process carried out by the research pharmacist. The pharmacist did not perform any study-related assessments or data analyses, and study investigators were blinded to randomization assignments. A log was kept by the research pharmacist, linking each individual with a unique identifier to either an active drug or a placebo group.

Participants received intradermal injections of either BoNT/B diluted to 2500U/mL or placebo (0.9% isotonic saline) by using a 30-G hypodermic needle. Each injection was evenly spaced every 4 to 6cm^2 in a grid pattern covering the surface area of the participant's residual limb that normally is in contact with their prosthetic socket. A measurement of the inside depth of the prosthetic socket was overlaid on the residual limb to determine the surface area of skin normally in contact with the socket. Each

participant received a total of 4mL of either BoNT/B or placebo per residual limb, except for 3 participants with 4 residual limbs that had been amputated at the transfemoral level. For these individuals, a total of 8mL was needed to give an equivalent dose per square centimeter of skin in contact with the prosthetic socket regardless of the site of amputation. Therefore, a total of 10,000U were used for individuals with transtibial amputation and 20,000U for those with transfemoral amputation. Before the injection, a topical anesthetic cream (30g of 4% topical lidocaine [EMLA]) or liberal amounts of topical anesthetic mist spray (Gebauer's Pain Ease) were applied to the residual limb according to manufacturer's instructions to ameliorate injection pain. After the injection, participants were instructed to continue to use whatever other sweat control treatments (eg, antiperspirants and oral medications) they had been using before the procedure, as needed. Participants were instructed to continue their pretreatment sweat control methods and to not vary these methods over the course of the study so that a variation would not affect results. At each follow-up visit, all participants confirmed that they had not varied their sweat control methods.

Gravimetric sweat analysis

Sweat production was objectively measured via gravimetric analysis. This involved weighing a filter paper before and after its use for absorbing perspiration. Before the injection, each participant was asked to exercise on a treadmill, which entailed walking with their prosthesis on at an exertion level of 11, or "light exertion" on the Borg Scale.[26] After exercise, their residual limb and the liner were covered with the filter paper (8.25-cm base) to absorb perspiration. After a total of 5 minutes, the filter paper from both the residual limb and the liner were removed and weighed, and the value obtained was subtracted from the weight of the dry filter paper to give the weight of the total sweat produced. This same procedure was repeated 4 to 6 weeks after the injection. The primary outcome measure used in this study was the proportion of participants achieving a minimum of 50% reduction in sweat production 4 to 6 weeks after the treatment.[16] Room temperature and percent humidity were measured and recorded at both the initial session and the follow-up assessment during the administration of the qualitative assessment, as well as the treadmill exercise test.

A qualitative assessment of sweating was also performed during each study visit. Participants completed a sweating assessment form (see supplemental appendix S1, available online only at http://www.archives-pmr.org/) that consisted of questions about the following: (1) perceived sweating; (2) perceived interference with prosthetic fit and function due to sweating; and (3) severity of PLP and RLP, all rated on a 100-mm visual analog scale (VAS).[27] In addition, participants were asked about side effects of the injection, pain perception of the procedure (measured using a 100-mm VAS), and any changes in the use of their prosthesis or prosthetic liner, as well as satisfaction with the treatment and likelihood to seek it out in the future and/or recommend it to a friend (measured using a Likert scale).[27,28]

Statistical analyses

Statistical analyses were performed for both the primary and the secondary objectives using SPSS version 21.[a] A repeated-measures analysis of variance was performed for each objective to test the equality of means. In addition, an independent *t* test was used to compare the percent changes in sweating between the BoNT/B and placebo groups. Significance was determined to be $P<.05$.

Results

Participants

A total of 9 male participants with either 1 or 2 major lower limb amputations (total 11 limbs) who complained of excessive sweating in their residual limb(s) were enrolled in the study between September 2010 and November 2012. The study population was randomly assigned to 2 groups: BoNT/B (n=7) or placebo (n=4) (tables 1 and 2). All participants were men with a mean age of 25.0±4.0 years and with lower limb amputation(s) at either the transfemoral (n=4) or the transtibial (n=7) level. In general, participants tended to be within 2 years of their amputation, and most of them reported wearing their prosthesis >8h/d.

Sweating

Gravimetric analysis

All participants (100%; 11) who received BoNT/B met the primary endpoint with respect to efficacy in sweat reduction, achieving a minimum of 50% reduction in sweat production 4 to 6 weeks after the treatment. The mean reduction for the BoNT/B group was −72.7%± 15.7%. Comparatively, 50% of participants (2) who received placebo met this primary endpoint with a mean reduction of only −32.7%± 39.2%. Furthermore, the efficacy in sweat reduction was statistically different between the 2 groups, with the BoNT/B group reporting a significantly greater reduction than did the placebo group ($P<.05$).

Gravimetric sweat analyses were significantly decreased for participants who received BoNT/B ($P<.05$) from a baseline assessment mean of 2.3±2.3g to a follow-up assessment mean of 0.7±1.1g. Participants who received placebo did not have a significant change in the amount of sweat produced (0.7±1.0 to 0.4±0.4g; $P>.05$) (fig 1).

Room temperature and percent humidity data revealed that for the BoNT/B group, the average temperature during the assessment

Table 1 Participants' demographic characteristics and prosthetic use information

Characteristic*	BoNT/B Group (n=7)	Placebo Group (n=4)	*P*
Age (y)	26.5±4.4	24.4±2.5	NA
Time since amputation (mo)	11±4.3	20±7.5	.109
Mean time of prosthetic use (mo)	8±3.8	12±5.8	.788
Sex			
Male	7 (100)	4 (100)	NA
Hours a day prosthesis is worn			.412
0–8	4 (57.1)	1 (25)	NA
≥8	3 (42.9)	3 (75)	NA
Runs with prosthesis	3 (42.9)	2 (50)	NA
Type of liner used			.758
Silicone	2 (28.6)	2 (50)	NA
Gel	3 (42.9)	2 (50)	NA
None	2 (28.6)	0 (0)	NA

NOTE. Values are mean ± SD or n (%).
Abbreviation: NA, not applicable.
* At the time of the baseline visit.

Table 2 Participants' demographic characteristics

Injection	Age (y)	Sex	Level of Amputation	Time Since Amputation (mo)	Total Dose (mL)
BoNT/B	24	Male	Transfemoral	8	8
BoNT/B	27	Male	Transtibial	4	4
BoNT/B	23	Male	Transtibial	13	4
BoNT/B	21	Male	Transfemoral	18	8
BoNT/B	24	Male	Transtibial	11	4
BoNT/B	33	Male	Transtibial	12	4
BoNT/B	33	Male	Transtibial	12	4
Placebo	26	Male	Transtibial	27	4
Placebo	27	Male	Transtibial	10	4
Placebo	21	Male	Transfemoral	18	8
Placebo	23	Male	Transfemoral	28	8

was 23.78°C with an average humidity of 33.21%; during the treadmill exercise test, temperature and humidity were 24.03°C and 33.61%, respectively. For the placebo group, the average temperature during the assessment was 23.32°C with a humidity of 43.5%; during the treadmill exercise test, temperature and humidity were 23.16°C and 43.3%, respectively. There is a difference of .46°C in the average temperatures of the testing environments of BoNT/B and placebo groups. Although there is a difference of 9.69% in the average humidity values of the testing environments of the 2 groups, at this low temperature the measured temperature is similar to the perceived temperature.[29] According to a Universal Scale of Apparent Temperature, at temperatures below 26.6°C the percent humidity does not affect the temperature perceived by the human body and so even with the differences in humidity the temperature in both rooms was experienced at the stated Celsius reading. Therefore, the difference in humidity has little effect on how much the participants perspired.

Qualitative self-report

Both BoNT/B and placebo groups reported a significant decrease in sweat measurements from baseline to follow-up assessments ($P<.05$ for both). For participants who received BoNT/B, perceived sweating measurements decreased from 74.3±24.5 to 37.1±26.1mm, whereas for participants who received placebo, perceived sweating measurements decreased from 75.0±14.1 to 39.5±30.0mm, as measured using a 100-mm VAS (fig 2). All participants, regardless of the treatment group, reported that the pain from the injection would not prevent them from receiving the study treatment in the future nor would it prevent them from recommending it to others. When asked about their satisfaction with the results of the treatment, all participants in both groups responded neutral to strongly satisfied, whereas none reported being dissatisfied or strongly dissatisfied with the treatment.

Secondary objectives

Interference with prosthetic function

Both BoNT/B and placebo groups reported a significant reduction in sweat interference with prosthetic function from their baseline assessment to their 4- to 6-week follow-up assessment, as measured by self-report using a 100-mm VAS ($P<.05$ for both).

Pain

Neither PLP nor RLP changed for either the BoNT/B group or the placebo group from baseline assessments to follow-up assessments ($P>.05$ for all).

Discussion

This study demonstrates that BoNT/B significantly reduces hyperhidrosis in the residual limbs of individuals with major lower limb amputation and that BoNT/B is a more effective treatment

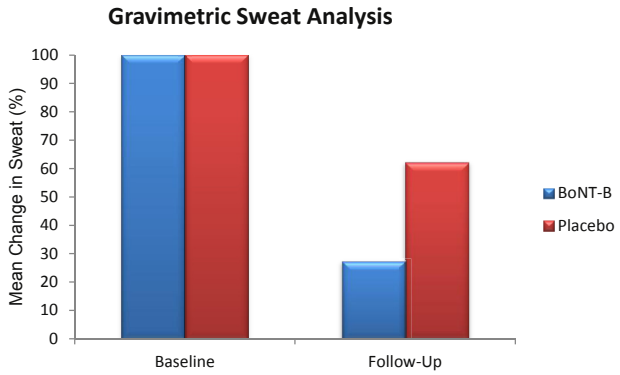

Fig 1 Gravimetric sweat analysis showed a greater percent reduction in the BoNT/B group (−67.3%±15.7%; n=7) than in the placebo group (−27.3%±39.2%; n=4).

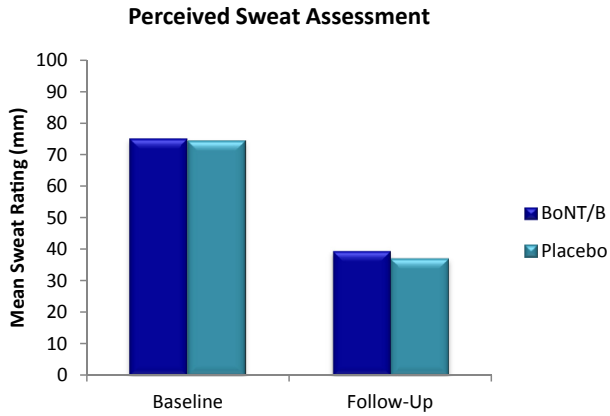

Fig 2 Perceived sweating assessment showed similar sweat measurements in both BoNT/B and placebo groups as measured by self-report using a 100-mm VAS.

than placebo at reducing sweating 4 to 6 weeks after the injection. All participants receiving BoNT/B injections exhibited a statistically meaningful decrease in the amount of sweat produced.

These results add to the body of literature expanding the clinical therapeutic applications for BoNT/B. Although BoNT/B is most commonly used to treat muscle disorders characterized by inappropriate muscle contractions, spasms, and increased tone,[30] its efficacy in treating other conditions, such as hyperhidrosis, warrants further attention, especially from rehabilitation professionals. BoNT/A (or Botox) has been used to successfully manage focal hyperhidrosis of the palms, feet, or axillae.[31-33] In a number of clinical studies,[5,15,34] BoNT/A has also proven effective in treating excessive sweating of the residual limbs of individuals with amputation. Only 1 pilot study thus far has explored the effect of the alternative serotype, BoNT/B, on the residual limb sweating in individuals with amputation. Kern[22] reported a significant reduction in sweating of the residual limb in a small case series of 9 individuals with amputation after 1750U BoNT/B injections; however, this study did not include a placebo group and relied on subjective self-report to measure efficacy.

To our knowledge, this study is the first double-blind, placebo-controlled, objectively measured pilot trial on the efficacy of BoNT/B in the treatment of residual limb hyperhidrosis. Gravimetric analysis of sweat production yielded data that were both unbiased and reproducible. Of interest, both groups (BoNT/B and placebo) reported a decrease in perceived sweating measurements from baseline to follow-up assessment. For the placebo group, this report of decreased sweating is in contrast to quantitative findings of no significant reduction. In addition, both groups after receiving the injections reported a significant decrease in sweat interference with prosthetic function, while neither group reported a statistically significant change in PLP or RLP over the course of treatment. These findings support the findings of Charrow et al,[5] who found that BoNT/A had no effect on the severity of RLP or PLP, but contrasted with the findings of Kern,[22] who showed that BoNT/B treatment leads to a decrease in RLP and PLP in individuals with limb amputation.

The unexpected finding that participants perceive a positive treatment effect, despite objective gravimetric analyses, suggests the presence of a strong placebo effect. Numerous studies[35,36] have demonstrated that participants who received placebo have clinical improvements identical or comparable to the changes caused by actual medication. Similarly, the placebo effect may have been a factor in the control participants' self-analysis of sweat interference with prosthetic function. This finding further indicates that subjective reports of improvement in prosthetic function require controlled trials to verify such findings.

Study limitations

There are several limitations to this pilot study. The small size of both groups indicates that the findings should be interpreted carefully in light of participants' demographic characteristics and study location. Our study population (mean age, 25.0±4.0y) was younger than the general population, and all participants were enlisted members of the military. It would be valuable to see this study replicated in an older, civilian population. Furthermore, limited long-term follow-up and fixed BoNT/B dosage preclude definitive conclusions about the dosage and injection frequency necessary to produce and maintain a positive response. Previous studies[22,37,38] have suggested that positive effects of BoNT/B last between 3 and 6 months. Most people will require repeated injections to have lasting effects, although it has also been reported that some people may develop immune resistance to the toxin and stop responding to treatment.[39,40] Future studies would benefit from confirmation of these findings on a larger scale. A larger sample size would also ensure greater similarity in baseline sweat profiles between groups, which is difficult to achieve with small participant samples. In addition, a comparison of BoNT/B with BoNT/A would be useful to determine which, if any, is more efficacious. Finally, by including an observation control group who receives no injection or has a run-in period, the role of time and prosthetic use in sweat production could be assessed more directly.

Conclusions

This prospective, double-blind, placebo-controlled pilot study demonstrates that BoNT/B effectively reduces hyperhidrosis in the residual limbs of individuals with lower level amputation at 4 to 6 weeks after the injection. In addition, BoNT/B is objectively more effective than placebo at reducing sweating in the residual limb, but does not affect PLP or RLP. No differences were found in perceived prosthetic function between BoNT/B and placebo groups. Further research is warranted to investigate the optimal dosage and frequency of BoNT/B injections into the residual limb and to assess the longevity of their effect.

Supplier

a. IBM Corp.

Keywords

Amputation; Hyperhidrosis; Rehabilitation; RimabotulinumtoxinB

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Supplemental Appendix S1 Sweating Assessment Form

Date: _____ Age: _____

1. Over the previous month, how much sweating have you experienced in your residual limb?

[Please place a single dash "/" on the line that represents your answer]

_____
None Very Much

2. Over the previous month, how much has the sweating interfered with your prosthesis functioning?

[Please place a single dash "/" on the line that represents your answer]

_____
None Very Much

3. Over the previous month, how much has the sweating interfered with your prosthesis fitting?

[Please place a single dash "/" on the line that represents your answer]

_____
None Very Much

4. Please mark what your average amount of phantom pain is over the previous month.

[Please place a single dash "/" on the line that represents your answer]

_____
None Worst Pain Ever

5. Please mark what your average amount of residual limb pain is over the previous month.

[Please place a single dash "/" on the line that represents your answer]

_____
None Worst Pain Ever

6. Date of amputation: _____

7. Date you began using a prosthesis on the limb with excessive sweating: _____

8. Approximately how many hours per day do you wear your prosthesis?

9. Approximately how many minutes per week do you **run** in your prosthesis?

10. Type of liner you are currently using most frequently: _____

11. Approximate amount of time you have been using this type of liner: _____

12. Type of suspension system (eg, pinlock, lanyard, suction, vacuum) you are currently using most frequently: _____

13. What other treatments for sweating have you tried (eg, antiperspirants, topical treatments such as aluminum chloride, oral medications, change in liner or suspension system)?

14. Of those treatments listed in item 13, which have you used in the previous week?

15. Please list all medications that you are currently taking: _____

16. Have you ever been treated with botulinum toxin, Dysport, Botox, or Myobloc?
Yes **No**

[THIS PAGE IS TO BE FILLED OUT AT THE END OF THE VISIT]

1. Make a tick mark along the scale below that represents the amount of pain you experienced related the injection of the medication.

_____

No pain **Worst possible pain**

2. Please describe the TYPE of pain that you experienced related to the injection of the medication. For example, “Sharp Pain,” “Dull Pain,” “Burning Pain,” “Stabbing Pain,”, OR USE YOUR OWN WORDS. You may use as many words to describe the pain as you like.

3. I would recommend this treatment to a fellow patient. (Circle one)

Strongly agree Agree Neutral Disagree Strongly disagree

4. The pain of the injections would prevent me from getting this treatment in the future. (Circle one)

Strongly agree Agree Neutral Disagree Strongly disagree

For follow-up visits ONLY:

5. I am satisfied with the results I experienced from receiving this treatment. (Circle one)

Strongly agree Agree Neutral Disagree Strongly disagree

6. I think this treatment helped reduce my sweating.

Strongly agree Agree Neutral Disagree Strongly disagree

[THIS PAGE IS TO BE FILLED OUT BY THE INVESTIGATOR]

Date: _____

Room temperature and humidity during questionnaire: _____

Target speed obtained in the treadmill walking phase: _____

Room temperature during the treadmill test: _____

Total weight of sweat produced in 5 minutes as measured by gravimetric analysis: _____

Pictures of residual limb with Minor’s (starch-iodine) test:

[Attach pictures here]

Number of vial used for injections: _____